02-25-02 JC07 Rec'd PCT/PTO 21 FEB 2002 PCT

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **PA-9948**

U S APPLICATION NO (IF KNOWN, SEE 37 CFR): **To be assigned 10/069690**

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/03373	**September 1, 2000**	**September 3, 1999**

TITLE OF INVENTION: **Improved Container Composition for Diagnostic Agents**

APPLICANT(S) FOR DO/EO/US: **Neil J. Rowley and Lewis R. Canning**

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U S.C. 1 821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4)
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

copy of this transmittal letter for charging purposes
return postcard

PCTUS1/REV03

U.S. APPLICATION NO (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
To be assigned 10/069690	PCT/GB00/03373	PA-9948

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**	
☒	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**	
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**	
☐	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	9 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $84.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**	
	TOTAL OF ABOVE CALCULATIONS =			**$890.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**	
	SUBTOTAL =			**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**	
	TOTAL NATIONAL FEE =			**$890.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
	TOTAL FEES ENCLOSED =			**$890.00**	
				Amount to be: refunded	$
				charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **500-588** in the amount of **$890.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **500-588** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Royal N. Ronning, Jr.
Amersham Biosciences Corp.
800 Centennial Avenue
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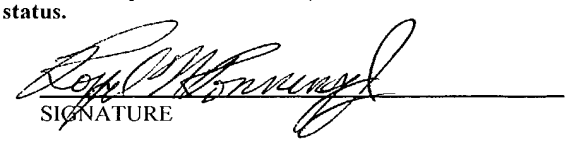


SIGNATURE

Royal N. Ronning, Jr.
NAME

32,529
REGISTRATION NUMBER

February 21, 2002
DATE

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): N. Rowley, et al.			Docket No. PA-9948
Serial No. 10/069690	Filing Date To be assigned	Examiner To be assigned	Group Art Unit To be assigned

Invention: **Improved Container Composition for Diagnostic Agents**

I hereby certify that the following correspondence:

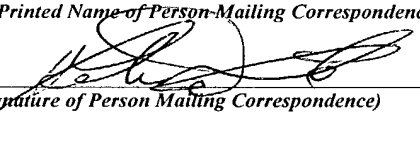
transmittal letter with copy, filing fee, first preliminary amendment, copy of the international application as published by the international bureau, copy of the international preliminary examination report, copy of the international search report, information disclosure statement without references, unsigned combined declaration/power of attorney, and a return postcard

(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

February 21, 2002
(Date)

Melissa Leck
(Typed or Printed Name of Person Mailing Correspondence)



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PA-9948

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	N. Rowley, et al.	Group Art Unit:	To be assigned
Serial Number:	To be assigned	Examiner:	To be assigned
Filing Date:	To be assigned		
Title:	Improved Container Composition for Diagnostic Agents		

First Preliminary Amendment

Honorable Assistant Commissioner of Patents
Box Patent Application
Washington, D.C. 20231

Sir:

Please consider the following amendments and remarks in connection with the prosecution of the captioned application, which is a filing under 35 U.S.C. § 371 and claims priority to international application number PCT/GB00/03373 filed September 1, 2000. This application also claims priority to patent application number 9920758.1 filed in Great Britain on September 3, 1999.

In the Claims

Please amend page 11, line 1, as follows:

[Claims]

What is claimed is:

Please amend claim 1 as follows:

1. (once amended) [A]In a composition which comprises a diagnostic agent in a container which has a silica coating on the inner surface, [characterised in that]the improvement comprising the diagnostic agent [comprises]including a non-radioactive metal complex or a hyperpolarised material.

Please amend claim 2 as follows:

2. (once amended) The composition of claim 1 [where]wherein the diagnostic agent [comprises]includes a non-radioactive metal complex.

Please amend claim 3 as follows:

3. (once amended) The composition of claim 2 [where]wherein the metal complex is an MRI contrast agent.

Please amend claim 4 as follows:

4. (once amended) The composition of claim 2 [where]wherein the metal complex is an X-ray contrast agent.

Please amend claim 5 as follows:

5. (once amended) The composition of claim 1 [where]wherein the diagnostic agent [comprises]includes a hyperpolarised material.

Please amend claim 6 as follows:

6. (once amended) The composition of claim 5 [where]wherein the hyperpolarised material [comprises]includes hyperpolarised ^{129}XE or ^{3}He gas.

Please amend claim 7 as follows:

7. (once amended) The composition of claim 5 [where]wherein the hyperpolarised material comprises one or more hyperpolarised ^{13}C atoms.

Please amend claim 8 as follows:

8. (once amended) The composition of [claims 1 to 7 where]claim 1 wherein the silica coating is deposited by PCVD.

Please amend claim 9 as follows:

9. (once amended) The composition of [claims 1 to 8 where]claim 1 wherein the silica coating comprises pure SiO_2

In the Abstract

Please add the following abstract on a separate sheet:

-- Abstract

The present invention relates to improved containers for diagnostic agents, which are metal complex contrast agents for MRI or X-ray imaging, or hyperpolarised materials where the container has an internal coating of SiO_2. The silica coating is preferably deposited by a plasma chemical vapour deposition (PCVD) process.--

Remarks

Claims 1-9 are pending in the instant application. Applicants have amended claims 1-9 to more fully conform with U.S. practice and to delete multiple dependencies. A version of the claims marked up to show the amendments, as well as a clean version of the claims encompassing the amendments, is attached hereto.

Applicants also request that the attached abstract be added to the specification on a separate sheet as required.

Applicants respectfully assert that all amendments are fairly based on the specification, and respectfully request their entry.

Applicants believe that the claims, as amended, are in allowable form, and earnestly solicit the allowance of claims 1-9.

Respectfully submitted,

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Attorney for Applicants

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Claims (marked up version showing amendments)

Page 11, line 1:

[Claims]

What is claimed is:

1. (once amended) [A]In a composition which comprises a diagnostic agent in a container which has a silica coating on the inner surface, [characterised in that]the improvement comprising the diagnostic agent [comprises]including a non-radioactive metal complex or a hyperpolarised material.

2. (once amended) The composition of claim 1 [where]wherein the diagnostic agent [comprises]includes a non-radioactive metal complex.

3. (once amended) The composition of claim 2 [where]wherein the metal complex is an MRI contrast agent.

4. (once amended) The composition of claim 2 [where]wherein the metal complex is an X-ray contrast agent.

5. (once amended) The composition of claim 1 [where]wherein the diagnostic agent [comprises]includes a hyperpolarised material.

6. (once amended) The composition of claim 5 [where]wherein the hyperpolarised material [comprises]includes hyperpolarised ^{129}XE or ^{3}He gas.

7. (once amended) The composition of claim 5 [where]wherein the hyperpolarised material comprises one or more hyperpolarised ^{13}C atoms.

8. (once amended) The composition of [claims 1 to 7 where]claim 1 wherein the silica coating is deposited by PCVD.

9. (once amended) The composition of [claims 1 to 8 where]claim 1 wherein the silica coating comprises pure SiO_2

Claims (clean version encompassing amendments)

What is claimed is:

1. (once amended) In a composition which comprises a diagnostic agent in a container which has a silica coating on the inner surface, the improvement comprising the diagnostic agent including a non-radioactive metal complex or a hyperpolarised material.

2. (once amended) The composition of claim 1 wherein the diagnostic agent includes a non-radioactive metal complex.

3. (once amended) The composition of claim 2 wherein the metal complex is an MRI contrast agent.

4. (once amended) The composition of claim 2 wherein the metal complex is an X-ray contrast agent.

5. (once amended) The composition of claim 1 wherein the diagnostic agent includes a hyperpolarised material.

6. (once amended) The composition of claim 5 wherein the hyperpolarised material includes hyperpolarised ^{129}XE or ^{3}He gas.

7. (once amended) The composition of claim 5 wherein the hyperpolarised material comprises one or more hyperpolarised ^{13}C atoms.

8. (once amended) The composition of claim 1 wherein the silica coating is deposited by PCVD.

9. (once amended) The composition of claim 1 wherein the silica coating comprises pure SiO_2

Abstract

The present invention relates to improved containers for diagnostic agents, which are metal complex contrast agents for MRI or X-ray imaging, or hyperpolarised materials where the container has an internal coating of SiO_2. The silica coating is preferably deposited by a plasma chemical vapour deposition (PCVD) process.

Improved Container Composition for Diagnostic Agents

Summary of the Invention

The present invention relates to improved containers for diagnostic agents, which are metal complex contrast agents for MRI or X-ray imaging, or hyperpolarised materials, where the container has an internal coating of silica (ie. silicon dioxide or SiO_2). The silica coating is preferably deposited by a plasma chemical vapour deposition (PCVD) process.

Field of the Invention

The present invention relates to diagnostic agents, especially for *in vivo* use, in a coated container, where the container has an internal coating of silica coating on the surface(s) which are in contact with the diagnostic agent.

Background to the Invention

US 4385086 (1983) discloses that a variety of materials (eg. soda glass, ceramics and metals) can be coated with highly oxidised silicon to prevent the leaching of metal ions from the material.

FR 2697014 A1 (1994) discloses the silica coating of the bottles, flasks, ampoules etc. for use with food or liquid pharmaceutical products to reduce leaching of metals into the liquid contents of the container.

DE 29609958 U1 discloses that glass containers having an internal coating of SiO_2 prepared by PCVD are useful for the storage of pharmaceutical or diagnostic solutions.

JP 11-99192A discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method), are useful to prevent adsorption of radiopharmaceutical products such as ^{201}Tl solution to the surface of the glass. The silica coating of these vials is manufactured by the method described in JP 2815595 B which involves treating the glass surface with a silyl tetraisocyanate vapour in a carrier gas, followed by heating at high temperatures. JP 2815595 B also discloses that such a silica coating is useful to prevent leaching of impurities such as alkali from the glass into medical products.

US 5612103 discloses the use of coatings of deuterated polymers to inhibit the depolarisation of hyperpolarised gases within a container. WO 99/08941 discloses the use of glass vessels coated with a sol-gel, preferably an aluminosilicate glass, for the same purpose. WO 99/17304 discloses the use of a container made of a special glass having a low iron content for the same purpose.

Summary of the Invention

The present invention relates to silica-coated containers in combination with the following categories of diagnostic agents:

(i) lyophilised kits or liquid or solution formulations for the preparation of MRI contrast agents which comprise metal complexes of paramagnetic metal ions;

(ii) lyophilised kits or liquid or solution formulations of X-ray contrast agents which comprise metal complexes of radiopaque metal ions;

(iii) hyperpolarised gases such as ^{129}Xe or ^{3}He or other hyperpolarised materials.

Detailed Description of the Invention

The present invention relates to a composition comprising a diagnostic agent in a container which has a silica coating on the inner surface. Suitable such containers are commercially available, e.g. a silica-coated vial called Silicoat is available from Fuji Glass KK, and a silica-coated vial called Type I Plus is available from Schott Glas. The Type I Plus vial is prepared by a plasma chemical vapour deposition (PCVD) process.

Other containers can be coated with silica using known methods, where the silicon-containing layer is deposited from either gas phase or liquid phase contact with the container surface(s), with optional pyrolysis and/or oxidation to convert the deposited silicon-containing layer to SiO_2. Such methods are known in the art. Using either approach, irregularly-shaped containers can be coated. Examples of gas phase deposition are PCVD, and the process of JP 2815595 B which uses silyl tetraisocyanate vapour in carrier gas. The latter process delivers the silicon-containing layer in a single step, with pyrolysis of silyl tetraisocyanate required to give the final product, i.e. the coated vial. Depending on the efficiency of the heat transfer, the coating layer may not be pure SiO_2, but perhaps contain carbon or nitrogen. The silica-coated vial prepared by PCVD has advantages over the disclosures of JP 2815595 B and JP 11-99192A, because the SiO_2 layer prepared by PCVD is in fact developed by multiple exposure to the vapour phase silicon reagent. The result is a much more uniform layer of high purity SiO_2, which is mechanically sound and resistant to abrasion etc. Hence PCVD is a preferred process for use in containers of the present invention.

The term "diagnostic agent" as used herein means either a hyperpolarised material or a non-radioactive metal complex which is an MRI contrast agent or an X-ray contrast agent. The "hyperpolarised material" can be a hyperpolarised gas, such as ^{129}Xe or ^{3}He, or a ^{13}C- or ^{15}N-enriched labelled molecule or a ^{19}F- or ^{31}P- containing molecule where the MRI active nucleus of interest has been hyperpolarised by a polarisation transfer process. The silica coatings of the present invention are believed to be especially useful for hyperpolarised ^{129}Xe compositions, since xenon has low solubility in silica. The diagnostic agent may be used for *in vivo* and/or *in vitro* diagnosis. The metal complex contrast agents of the present invention are preferably for *in vivo* use.

The term "metal complex" as used herein means a coordination complex of a metal (M) with an organic ligand (L). This is to be contrasted with an uncomplexed or free metal ion e.g. the monovalent thallium cation Tl^{+}. The term 'organic ligand' as used herein means a carbon-containing compound which comprises at least one heteroatom suitable for coordination to a metal, such as N, O, S, P or Se, or combinations thereof. Examples of organic ligands are amines, hydrazines, ethers such as crown ethers, thiols or thioethers, oximes, phosphines, amides, pyridines or other heterocyclic molecules such as quinolines, aminocarboxylate ligands such as DTPA, DOTA or HEDTA. The metal donor atoms can be arranged together to form chelating agents or polydentate ligands such as diaminedioximes, hydroxyquinolines, diaminedithiols, diamidedithiols; or macrocyclic ligands such as DOTA, and many more combinations as is well known in the art. MRI contrast agents are typically metal complexes, where the metal is a paramagnetic metal ion such as gadolinium (III) of aminocarboxylate ligands such as DTPA or DOTA. X-ray contrast agents can also be metal complexes, where the metal is radiopaque, such as bismuth or tungsten.

When the diagnostic agent is or comprises a metal complex, if leached metal ions (M') such as aluminium or sodium, are leached from glass into the product, these leached metal ions may adversely affect the product in a manner which goes beyond the simple presence of M' as an impurity:

(i) $ML_n + M' \rightarrow M'L_q + M$ ligand exchange or transmetallation

(ii) $L + M' \rightarrow M'L_q$ complexation

where:

M is the metal of the desired metal complex product,

L is the organic ligand;

M' is the leached metal ion;

ML_n is the metal complex product, which may comprise 2 or more different organic ligands L;

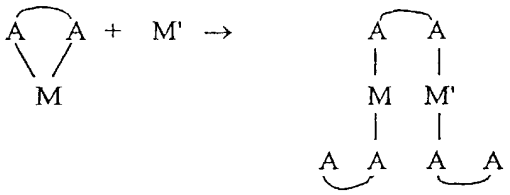
n is number of ligands (L) attached to M and is an integer of value 1 to 8;

$M'L_q$ is the metal complex impurity;

q is number of ligands (L) attached to M' and is an integer of value 1 to 8.

Process (i) can occur when the leached metal or metals (M') have greater affinity for one or more of the organic ligands (L) than the metal (M) of the contrast agent product. In addition to, or instead of equation (i), complexation (ii) may also occur. This leads to the presence of undesirable $M'L_q$ impurities in the product ML_n.

When L is a multidentate ligand, such as a chelating agent the number of metal donor sites (A) per ligand (L) may be 2, 3, 4, 5, 6 or 8 typically. In that case, a process which is a special case of equation (i) above could occur as follows:

(iii) 

where: the free A donors can complex to further M/ M' atoms etc.

note: the curved lines represent the chain of atoms linking the A groups.

leading to dimeric or oligomeric binuclear or polynuclear metal complexes involving both M and M'. The leached metal (M') may be less amenable to chelation by polydentate ligand (L), and hence favour such polynuclear species, even when M does not. This could result when the energetics are less favourable, e.g. M' is too small for two A groups to coordinate without undue steric interactions. In this way, a single M' atom could potentially generate a polynuclear or oligomeric species which comprises several M atoms. Clearly, the greater the denticity of the ligand L (i.e. the greater the number of A metal donor sites), the greater the potential complexity of the product.

The presence of such species may present impurity or manufacturing or irreproducibility problems due to vial-to-vial variations, or toxicity problems due to the impurity species or particulate problems when insoluble materials result, eg. when $M'L_q$ is highly insoluble. Such insoluble impurities may also potentially serve to promote co-precipitation of the desired product ML_n. Particulate problems would be a serious safety problem for products intended for human injection. Impurity species may also adversely

affect product imaging performance by e.g. localising in undesirable background areas *in vivo* which adversely impact the image to be made.

In the light of the above, it can be seen that the influence of leachable metal ions (M'), can have effects which go far beyond simply the presence of metal ion impurities alone in solution. This is important for metal complex contrast agent products, and is not recognised by JP 11-99192A which makes no specific reference to metal complexes. The ^{201}Tl radioisotope taught by JP 11-99192 A is an uncomplexed radiometal in the chemical form of the Tl(I) cation Tl^+. The teaching of JP 11-99192 A relates only to adsorption effects *via* an ion exchange mechanism for the ^{201}Tl cation Tl^+ with the non-radioactive Na^+ and K^+ ions of the glass container walls. The main thrust of JP 11-99192 A is to a radiopharmaceutical vial having reversed text characters on the surface of the container.

For uncoated glass containers, the leaching of metal ions from the glass can potentially be overcome by washing with dilute aqueous acid solutions (to remove relatively labile leachable metal ions), following by rinsing and (optionally) drying steps, before the container is loaded with product. The layer of SiO_2 suppresses any such leaching of metal ions (M'), and hence obviates the need for any such washing steps. This is particularly important for diagnostic products intended for human use, especially for human injection, since these washing steps must be done in a sterile manner, hence although such steps may be straightforward, their removal represents a significant improvement.

Hyperpolarised materials are non-radioactive materials which have a finite lifetime due to the decay process from the hyperpolarised state to the ground state, i.e.

depolarisation. The rate of depolarisation is believed to be increased in the presence of paramagnetic species, especially molecular oxygen, or paramagnetic metal ions e.g. Fe^{3+}. The composition of the present invention where the diagnostic agent is a hyperpolarised material, therefore provides improved containers where an inert layer of essentially pure SiO_2 is interposed between the hyperpolarised material and the normal walls of the container.

The SiO_2 layer is free from any metallic ions or paramagnetic species and is of high chemical purity, especially when it is deposited by CPVD. It is hence expected to represent an improvement over prior art approaches to increasing the lifetime of hyperpolarised species.

Silica coating techniques based on gas phase deposition, eg. PCVD, can be adapted to coat the inner surfaces of containers or vessels of almost any shape or size. Hence it is anticipated that the container compositions of the present invention can be applied to production apparatus as well as storage and transport vessels. The silica coating can also readily be applied to non-rigid, flexible materials such as thin plastics. Such containers could be used e.g. for containing doses of hyperpolarised gases such as ^{129}Xe or ^{3}He in plastic bags with an inner silica coating, as unit doses for human administration by inhalation.

Example 1 shows that a silica-coated vial (the Type 1 Plus vial) does prevent the leaching of silicon, sodium, aluminium and boron ions from the glass, even under stress conditions.

Experimental

Example 1

Groups of 10 Type I Plus vials (Schott Glas) were subjected to a series of stress tests to demonstrate the robustness of the silica coating with respect to leachable ions. The basic test was the resistance of the coating to the leaching of cations when autoclaved with 0.04M aqueous HCl. This test was performed after vials were exposed to the following stress conditions:

1. vials were washed, and then pyrogen baked. 2ml of 0.04M HCl was added and the vials sealed. Test vials were autoclaved, then stored upright at 40°C before testing for leachable cations.
2. vials were stored for 6 weeks at -196°C, then washed and pyrogen baked. 2ml of 0.04M HCl was added to each vial, and the vials were then sealed, autoclaved and tested for leachable cations.
3. as for test 2, except that the vials were stored at -70°C, -20°C, +20°C and +40°C/75% relative humidity.
4. further tests included: vials pyrogen baked 3 times; vials containing 0.04M HCl autoclaved three times; vials gamma irradiated (35.4 – 36.2 kGy dose).

All test solutions were measured by ICP for silicon, sodium, aluminium and boron, those cations considered to be most leachable from the vial surface. The results are given in Table 1.

Table 1

Test Number		Si	Na	Al	B
1		0.149	Nd	0.006	Nd
2		0.163	Nd	Nd	Nd
3	-70°C	0.167	Nd	Nd	Nd
	-20°C	0.193	0.005	0.002	0.002
	+20°C	0.193	0.009	0.005	0.003
	+40°C	0.236	0.006	0.002	0.002
4	bake	0.110	Nd	0.010	Nd
	X3	0.378	0.012	Nd	0.006
	Gamma	0.102	0.003	Nd	Nd

Note: each table entry is the mean of 12 batch runs, each batch of 10 vials (i.e. 120 vials tested), expressed in $\mu g/cm^3$ of test solution.

Nd = not detected. Detection limits (in $\mu g/cm^3$): B – 0.004
Si – 0.003
Na – 0.004
Al – 0.004

Claims

1. A composition which comprises a diagnostic agent in a container which has a silica coating on the inner surface, characterised in that the diagnostic agent comprises a non-radioactive metal complex or a hyperpolarised material.

2. The composition of claim 1 where the diagnostic agent comprises a non-radioactive metal complex.

3. The composition of claim 2 where the metal complex is an MRI contrast agent.

4. The composition of claim 2 where the metal complex is an X-ray contrast agent

5. The composition of claim 1 where the diagnostic agent comprises a hyperpolarised material.

6. The composition of claim 5 where the hyperpolarised material comprises hyperpolarised ^{129}Xe or ^{3}He gas.

7. The composition of claim 5 where the hyperpolarised material comprises one or more hyperpolarised ^{13}C atoms.

8. The composition of claims 1 to 7 where the silica coating is deposited by PCVD.

9. The composition of claims 1 to 8 where the silica coating comprises pure SiO_2.

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(54) Title: IMPROVED CONTAINER COMPOSITION FOR DIAGNOSTIC AGENTS

(57) Abstract: The present invention relates to improved containers for diagnostic agents, which are metal complex contrast agents for MRI or X-ray imaging, or hyperpolarised materials where the container has an internal coating of SiO_2. The silica coating is preferably deposited by a plasma chemical vapour deposition (PCVD) process.

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Declaration Submitted After Initial Filing

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Improved Container Composition for Diagnostic Agents

the specification of which

[ ] is attached hereto.
OR
[X] was filed on **September 1, 2000** as United States Application No.or PCT International Application No. **PCT/GB00/03373** and was amended on _____ _____.(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or (f) or Section 365 (b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign applications for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

9920758.1	**Great Britain**	**03 September 1999**
(Number)	(Country)	(Day/Month/Year Filed)

I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this

application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, CFR Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

PCT/GB00/03373	**01 September 2000**
(Application Serial No.)	(Filing Date)

As a named inventor, I hereby appoint the following attorneys or agents to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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